Regular Article

Minocycline combination therapy with fluvoxamine in moderate-to-severe obsessive–compulsive disorder: A placebo-controlled, double-blind, randomized trial

Sophia Esalatmanesh, MD,[1†] Zoha Abrishami, MD,[1†] Atefeh Zeinoddini, MD,[1†] Fatemeh Rahiminejad, MD,[1] Majid Sadeghi, MD,[1] Mohammad-Reza Najarzadegan, MD,[2] Mohammad-Reza Shalbafan, MD[2] and Shahin Akhondzadeh, PhD[1]*

[1]*Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences,* [2]*Mental Health Research Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran*

Aim: Several lines of evidence implicate glutamatergic dysfunction in the pathophysiology of obsessive–compulsive disorder (OCD), presenting this neurotransmitter as a target for the development of novel pharmacotherapy. The objective of this study was to assess the efficacy of minocycline as an augmentative agent to fluvoxamine in the treatment of patients with OCD.

Methods: One hundred and two patients with the diagnosis of moderate-to-severe OCD were recruited to this study. A randomized double-blind trial was designed and patients received either L-carnosine or placebo as adjuvant to fluvoxamine for 10 weeks. The patients randomly received either minocycline 100 mg twice per day or placebo for 10 weeks. All patients received fluvoxamine (100 mg/day) for the first 4 weeks, followed by 200 mg/day for the rest of the trial, regardless of their treatment groups. Participants were evaluated using the Yale–Brown Obsessive Compulsive Scale (Y-BOCS). The main outcome measure was to assess the efficacy of minocycline in improving the OCD symptoms.

Results: General linear model repeated measures demonstrated significant effect for time × treatment interaction on the Y-BOCS total scores, $F(1.49, 137.93) = 7.1$, $P = 0.003$, and Y-BOCS Obsession subscale score, $F(1.54, 141.94) = 9.72$, $P = 0.001$, and near significant effect for the Y-BOCS Compulsion subscale score, $F(1.27, 117.47) = 2.92$, $P = 0.08$. A significantly greater rate of partial and complete response was observed in the minocycline group ($P < 0.001$). The frequency of side-effects was not significantly different between the treatment arms.

Conclusion: The results of this study suggest that minocycline could be a tolerable and effective adjuvant in the management of patients with OCD.

Key words: fluvoxamine, glutamate, minocycline, obsessive–compulsive disorder, trial.

OBSESSIVE–COMPULSIVE DISORDER (OCD) affects 1–3% of the world population. Generally, it has an early age onset during childhood or early adult life.[1–3] The course of illness is waxing and waning chronically if left untreated.[4,5] OCD severely impairs quality of life in patients.[6] Cognitive-behavioral therapy in the form of exposure and response prevention (ERP) and medication management are the mainstay of treatment for OCD. OCD first-line medications are serotonin reuptake inhibitors (SRI).[7,8] SRI usually decrease the severity of OCD symptoms by as much as 20–30%.[9] Satisfactory treatment is obtained in 40–60% of OCD patients.[10–12] Therefore, focus of many trials has been

*Correspondence: Shahin Akhondzadeh, PhD, Psychiatric Research Center, Roozbeh Psychiatric Hospital, Tehran University of Medical Sciences, South Kargar Street, Tehran 13337, Iran.
Email: s.akhond@neda.net
†The first three authors contributed equally to this study.
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on the development of novel agents in the pharmacotherapy of OCD.[11–15] Several lines of evidence suggest that OCD can be caused by glutamatergic dysfunction in orbitofrontal/basal ganglia brain circuits.[16,17] Neuroimaging studies demonstrated reduction of glutamatergic neurotransmission in the anterior cingulate cortex of OCD patients.[18] Glutamate in the cerebrospinal fluid (CSF) of OCD patients is increased and this provides evidence in support of the neurobiological models of OCD.[19] In previous studies, 30–54% of OCD patients responded to glutamate modulators as an augmentation agent to SRI.[20–24] Minocycline is the most widely prescribed antibiotic for chronic acne due to lower antibiotic resistance compared to other tetracyclines and antimicrobials.[25] Minocycline passes the blood–brain barrier. Prior trials have shown neuroprotective effects of minocycline in amyotrophic lateral sclerosis and Parkinson's disease.[26,27] In animal studies, minocycline has been reported to significantly reduce 3,4-methylenedioxymethamphetamine-induced neurotoxicity of 5-hydroxytryptamine and dopamine systems in the cerebral cortex and hippocampus and to promote neurogenesis.[28] Minocycline has a regulatory effect on pro-inflammatory agents, including nitric oxide, tumor necrosis factor-α, and interleukin-1β.[29] Animal studies have shown that minocyclines decrease glutamate-induced neurotoxicity.[30] Minocycline has therapeutic effects on neurodegenerative diseases and this might be achieved through the blockade of glutamate-mediated excitotoxicity.[31] Moreover, this antibiotic is known for its antioxidant and anti-inflammatory characteristics, which could further explain its neuroprotective effects.[32] Previously, we have demonstrated the beneficial role of minocycline in improving symptoms of schizophrenia, depressive and autistic symptoms.[33–35] The present study was conducted to investigate the efficacy and safety of minocycline as an augmentative agent to fluvoxamine, an SRI strongly supported by OCD randomized trials in treatment of moderate-to-severe OCD patients.[36,37]

METHODS

Trial setting and design

A 10-week, single-center, randomized, double-blind, placebo-controlled, parallel-group trial was performed in the outpatient clinic of Roozbeh Psychiatric Hospital (teaching hospital of Tehran University of Medical Sciences, Tehran, Iran) from March 2015 to January 2016. The trial was approved by the ethics committee of Tehran University of Medical Science (Grant No.: 27224) and conducted according to the Declaration of Helsinki and subsequent revisions. Written informed consent was obtained from all subjects before participation. Patients were informed that their participation was voluntary and that they could withdraw from the trial at any time with no negative effect on their treatment. The trial was registered at the Iranian Registry of Clinical Trials (www.irct.ir; registration number: IRCT201501031556N70).

Participants

Patients, aged 18–50 years, with a clinical diagnosis of OCD according to the DSM-IV-TR, were screened for the study. Those with a diagnosis of moderate-to-severe OCD defined by a Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥21 were included.[38,39]

Patients were excluded from the study if they had any other comorbid DSM-IV axis I disorders, serious medical or neurological condition, substance dependence (other than caffeine or nicotine), mental retardation (based on clinical judgment), pregnancy, breast-feeding, or any contraindication for the use of minocycline or fluvoxamine, hepatic or renal disease, seizure, lupus, neutropenia, anemia, thrombocytopenia, head trauma, history of previous psychosurgery for OCD, or any hypersensitivity to the tetracycline antibiotics group. During the course of the trial, patients were not allowed to participate in psychotherapeutic sessions. Patients were also excluded if they had received any psychotropic drugs in the previous 6 weeks.

Interventions

Eligible participants were randomized to receive either minocycline (Hexal, 100-mg tablet), 100 mg twice per day, or placebo for 10 weeks. All participants, regardless of group assignment, also received fluvoxamine (Sobhan, 50-mg and 100-mg tablets), 100 mg/day for 28 days, followed by 200 mg/day for the rest of the trial.

Outcome

Y-BOCS was used to evaluate treatment efficacy. This is a well-validated 10-item rating scale, which is

widely used to measure the severity of OCD symptoms and has also been applied in several clinical trials in Iran.[11–14] Participants were rated by Y-BOCS at baseline and at weeks 4 and 10.

The main outcome measure was difference in score change of the Y-BOCS total score from the baseline to the end of the trial between the two groups. Differences in score change of the Y-BOCS Obsession and Compulsion subscales from baseline to week 10 as well as differences in score change of total and subscale scores from baseline to other time-points were assigned as secondary outcome measures. Other secondary outcome measures included differences in partial response rates (defined as ≥25% reduction in Y-BOCS score), complete response rates (≥35% reduction in Y-BOCS score) and remission rates (score ≤16) between the two groups.[40] Regarding the adverse events, participants were strongly encouraged to contact the study team about any unexpected adverse events occurring during the use of the drugs. Adverse events were recorded using a structured checklist at each visit. Participants were first asked an open-ended question about the occurrence of any adverse event. Furthermore, all patients received a phone call 1 week after treatment initiation to evaluate possible adverse effects. All participants underwent a thorough physical examination and measurement of a complete blood count (CBC), liver and kidney function test values at baseline and at each post-baseline visit.

Sample size

With the assumption of a difference of four points on Y-BOCS scores between the minocycline and the placebo groups, an SD of 5, a two-sided significance level of 0.05, and a statistical power of 95%, a sample size of 84 (each group 42) was calculated. Predicting a dropout rate of 20%, a total number of 102 participants were needed.

Randomization, allocation concealment, and blinding

A computerized random-number generator was used to allocate patients into two groups in a 1/1 ratio (blocks of 4). The assignments were concealed in sequentially numbered sealed, opaque envelopes. Minocycline and placebo capsules had similar appearance, shape, size, texture, color and odor. Random allocation was performed by an independent person who was not involved elsewhere in the trial. The patients, the psychiatrists who rated them and prescribed the medication, and the statistician were all blind to allocation.

Statistical analysis

Data analysis was carried out using SPSS 22 (SPSS, Chicago, IL, USA). Numerical variables were summarized by using mean ± SD and categorical variables were presented as number of patients and percentages. Normally distributed continuous variables were compared between the minocycline and the placebo groups using the Independent *t*-test. The mean difference (MD) between the minocycline group and the placebo group was reported as MD, 95% confidence interval (CI). Two-factor repeated-measure ANOVA was used to evaluate time × treatment interaction between the treatment groups. The Greenhouse–Geisser adjustment was performed, when Mauchly's test of sphericity indicated that the assumption of sphericity had been violated. After controlling for baseline Y-BOCS scores, ANCOVA was used to compare Y-BOCS scores between the groups at the trial end. Cohen's *d* effect size was calculated to quantify the treatment effect. The χ^2 or Fisher's exact tests were used to compare proportions between the two groups as appropriate. All of the above-mentioned statistical analyses were performed two-sided, and $P < 0.05$ was considered as significant.

RESULTS

Patients

A total of 126 patients were screened for eligibility criteria. One hundred and two patients were randomly assigned to receive either minocycline plus fluvoxamine ($n = 51$) or placebo plus fluvoxamine ($n = 51$). Eight patients discontinued the trial (four patients in each group) and a total of 94 patients (47 in each group) completed the trial (Fig. 1). Baseline characteristics of the participants are summarized in Table 1. At baseline, no patient suffered from an infective disease that needed antibiotic usage.

Y-BOCS total score

Y-BOCS total scores did not differ significantly between the two groups at baseline, MD (95%CI) = 0.36 (−0.90

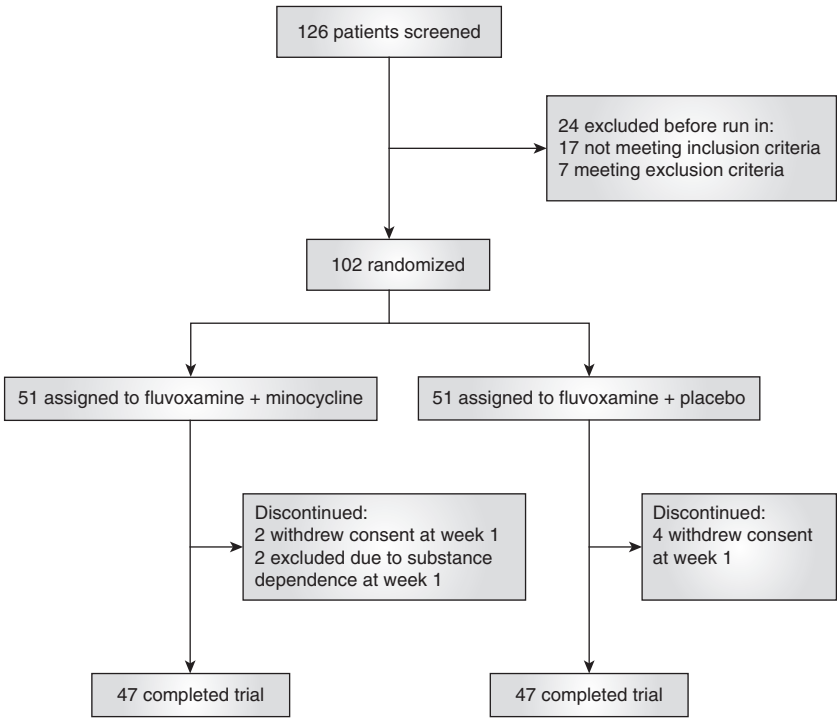

Figure 1. Flow diagram of the study.

Table 1. Baseline characteristics according to the treatment group

	Minocycline group (n = 47)	Placebo group (n = 47)	P-value
Age (years), mean ± SD	34.65 ± 7.96	34.04 ± 8.90	0.72
Sex, female, n (%)	29 (61.7%)	29 (61.7%)	1.00
Duration of the disease (years), mean ± SD	4.48 ± 2.61	5.27 ± 2.92	0.17
Education			
Primary and secondary school	14 (29.8%)	16 (34.0%)	NS
Diploma	23 (48.9%)	15 (31.9%)	
University degree	10 (21.3%)	16 (34%)	
Single : married	15 (31.9%):32 (68.1%)	20 (42.6%):27 (57.4%)	0.28
Y-BOCS total score, mean ± SD	29.93 ± 4.03	29.57 ± 1.58	0.56
Y-BOCS Obsession subscale score, mean ± SD	15.93 ± 2.14	15.42 ± 1.19	0.15
Y-BOCS Compulsion subscale score, mean ± SD	13.93 ± 2.64	14.14 ± 0.97	0.60

NS, not significant; Y-BOCS, Yale–Brown Obsessive Compulsive Scale.

to 1.62), t (59.86) = 0.57, P = 0.56. Significant effect for time × treatment interaction, Greenhouse–Geisser corrected: F(1.49, 137.93) = 7.1, P = 0.003 (Fig. 2), was demonstrated by repeated-measure ANOVA. ANCOVA demonstrated significantly lower scores in the minocycline group compared to the placebo group at the end of the trial course, F(1, 91) = 7.24, P = 0.008 (Table 2), after controlling for baseline Y-BOCS total score. At the end of the trial, significantly higher remission rate, partial and complete response rates were observed in the minocycline group compared to the placebo group (Table 3). A significantly shorter

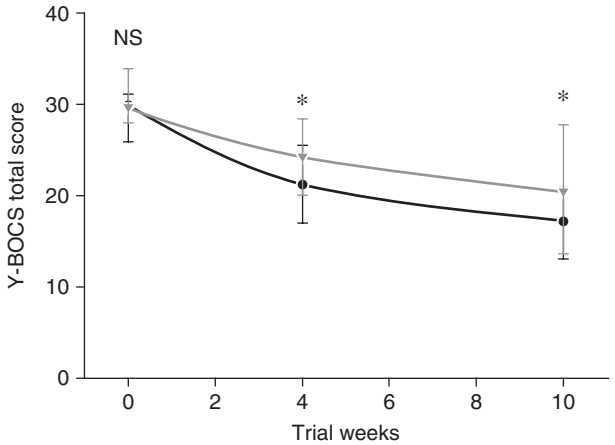

Figure 2. Repeated-measure analysis of variance for the effect of two treatments on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) total scores. *P*-values show the result of the analysis of covariance for comparison of scores between the two groups at each time interval after controlling for baseline scores (mean ± SD; $^{*}P < 0.05$). NS, not significant. (—•—) Minocycline group. (—▿—) Placebo group.

time was needed in the minocycline group than the placebo group for partial response ($P < 0.001$), as demonstrated by the Kaplan–Meier estimation (Fig. 3).

Y-BOCS Obsession subscale score

At baseline, Y-BOCS Obsession subscale scores did not differ between the two groups, MD (95%CI) = 0.51 (−0.20 to 1.22), t (72.06) = 1.42, $P = 0.15$. General linear model repeated measure demonstrated significant effect for time × treatment interaction on Y-BOCS total score, $F(1.54, 141.94) = 9.72$, $P < 0.001$ (Fig. 4). ANCOVA, after controlling for baseline Y-BOCS Obsession subscale score, demonstrated lower scores in the minocycline arm in comparison with the placebo arm at the end of the trial course, $F(1, 91) = 9.81$, $P = 0.002$ (Table 2).

Y-BOCS Compulsion subscale score

At baseline, Y-BOCS Compulsion subscale scores did not differ between the two groups, MD (95% CI) = −0.21 (−1.03 to 0.61), t (58.30) = −0.51, $P = 0.60$. General linear model repeated measure demonstrated a near significant effect for time × treatment interaction on Y-BOCS total score, F (1.27, 117.47) = 2.92, $P = 0.08$ (Fig. 5). ANCOVA, after controlling for baseline Y-BOCS Compulsion subscale score, demonstrated lower scores in the minocycline group arm in comparison with the

Table 2. Comparison of the Y-BOCS total and subscales scores between two groups using analysis of covariance

Y-BOCS score	Minocycline group (n = 47)	Placebo group (n = 47)	Mean differences minocycline–placebo (95%CI)	Cohen's d	P-value
Total (week 10)	17.21 ± 3.57	20.42 ± 7.35	3.21 (0.84–5.58)	0.56	0.008
Obsession (week 10)	8.53 ± 2.34	10.69 ± 4.12	2.12 (0.75–3.50)	0.64	0.002
Compulsion (week 10)	8.23 ± 1.96	9.76 ± 4.09	1.53 (0.21–2.84)	0.48	0.02

CI, confidence interval; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Table 3. Comparison of outcome indexes between the two groups

Outcome	Minocycline group	Placebo group	P-value	Odds ratio (95%CI)
Number (%) of PR at week 4	29 (61.7%)	12 (25.5%)	<0.001	4.69 (1.94–11.33)
Number (%) of PR at week 10	40 (85.1%)	18 (38.3%)	<0.001	9.20 (3.40–24.90)
Number (%) of CR at week 4	11 (23.4%)	8 (17.0%)	0.44	1.49 (0.53–4.11)
Number (%) of CR at week 10	36 (76.6%)	15 (31.9%)	<0.001	6.98 (2.80–17.38)
Number (%) of remitters at week 4	7 (14.9%)	5 (10.6%)	0.53	1.47 (0.43–5.01)
Number (%) of remitters at week 10	23 (48.9%)	13 (27.7%)	0.03	2.50 (1.06–5.90)

CI, confidence interval; CR, complete responders; PR, partial responders.

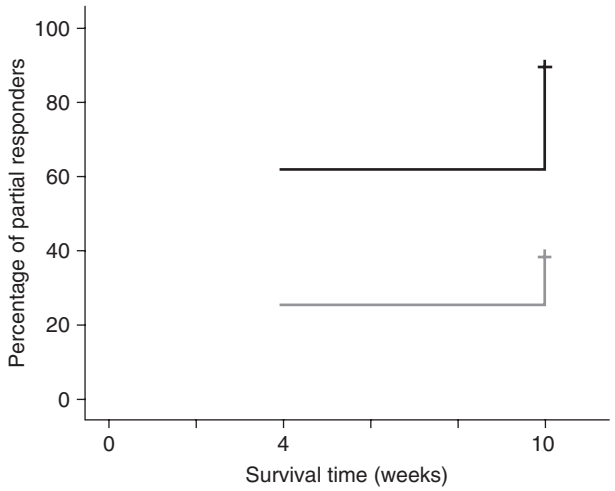

Figure 3. Comparison of time needed to partially respond to treatment between the two groups. (⌐¬) Minocycline group. (⌐¬) Placebo group.

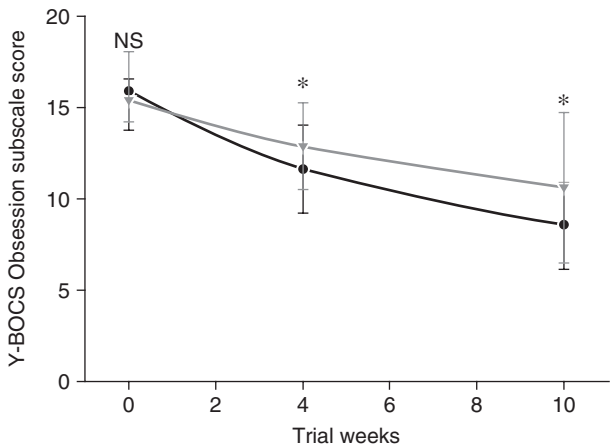

Figure 4. Repeated-measure analysis of variance for the effect of two treatments on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) Obsession subscale scores. *P*-values show the result of the analysis of covariance for comparison of scores between the two groups at each time interval after controlling for baseline scores (mean ± SD; $^{*}P < 0.05$). NS, not significant. (—•—) Minocycline group. (—▾—) Placebo group.

placebo arm at the end of the trial course, $F(1, 91) = 5.04$, $P = 0.02$ (Table 2).

Side-effects

Adverse events were recorded during the study. Side-effects were mild and did not result in withdrawal.

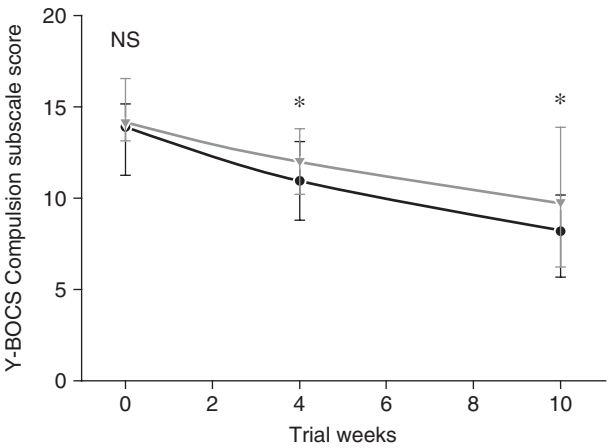

Figure 5. Repeated-measure analysis of variance for the effect of two treatments on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) Compulsion subscale scores. *P*-values show the result of the analysis of covariance for comparison of scores between the two groups at each time interval after controlling for baseline scores (mean ± SD; $^{*}P < 0.05$). NS, not significant. (—•—) Minocycline group. (—▾—) Placebo group.

Frequency of side-effects was not different between the two groups (Table 4).

DISCUSSION

OCD results in impaired social and occupational function of the patients.[6] Data suggest that OCD can be caused by glutamatergic dysfunction in orbitofrontal/basal ganglia brain circuits.[16,17] There is increasing interest in augmentative strategies because

Table 4. Frequency of adverse events between treatment groups

Adverse event	Minocycline group (n = 47)	Placebo group (n = 47)	*P*-value
Diarrhea, *n*, %	6 (12.8)	3 (6.4)	0.48
Headache, *n*, %	4 (8.5)	3 (6.4)	1.00
Increased appetite, *n*, %	5 (10.6)	7 (14.9)	0.53
Dizziness, *n*, %	4 (8.5)	5 (10.6)	1.00
Insomnia, *n*, %	3 (6.4)	4 (8.5)	1.00
Nausea, *n*, %	6 (12.8)	4 (8.5)	0.50
Sedation, *n*, %	5 (10.6)	6 (12.8)	0.74
Abdominal pain, *n*, %	6 (12.8)	4 (8.5)	0.50

a significant number of OCD patients do not adequately respond to the first-line medication. Rosenberg *et al.* suggested a reversible glutamatergically mediated impairment of the thalamo-cortical-striatal pathway in OCD patients.[41] Minocycline has neuroprotective effects in different neurological diseases.[42] Kuloglu *et al.* demonstrated a significantly higher level of malondialdehyde, a product of lipid peroxidation, and glutathione peroxidase in OCD patients compared to the control group.[43] Experimental studies have consistently provided support for a deficient glutathione oxidative protective system in the animal model of OCD, especially in the frontal cortex.[44] The beneficial effect of minocycline in OCD patients is partly due to its anti-oxidative characteristics, as oxidative stress is known to be associated with OCD.[45,46]

Several lines of evidence implicate that OCD can be caused by glutamatergic dysfunction in orbitofrontal/basal ganglia brain circuits.[47] These evidences can be categorized into three main groups: (i) the observation of changes in glutamate concentrations as assessed from CSF or by magnetic resonance spectroscopy of the caudate anterior cingulate cortex in patients with OCD; (ii) studies on animal models with impaired glutamate signaling and concurrent phenotype resembling OCD; and (iii) the finding of variations in genes involving the glutamate pathway in patients with OCD.[48] Studies have shown significantly higher glutamate concentrations on the CSF of patients with OCD compared to controls.[19,49] Rosenberg *et al.* studied 11 psychotropic drug-naïve children with OCD and showed significantly higher caudate glutamate concentrations in patients in comparison with healthy controls.[50] Inhibiting glutamate release has been associated with reduction in OCD-like behavior in mice,[51,52] and glutamate system dysregulation marked by increased glutamate has been linked to compulsive or repetitive behaviours.[53] The neuroprotective effect of minocycline against glutamate excitotoxicity, through regulation of the p38 and Akt pathways, is probably another mechanism by which minocycline improves symptoms in patients with OCD.[31] The advantages of minocycline include low cost and US Food and Drug Administration approval in adults and children >12 years.[25] It has an excellent side-effect profile. In a long-term placebo-controlled trial, minocycline was given to Huntington's disease patients for 2 years and it was well-tolerated, with no serious adverse effects.[48] Previous studies have demonstrated the beneficial role of glutamate modulators, such as riluzole and memantine, as augmentation agents to SRI.[20–24,53–56] An open-label augmentation trial of memantine, as a glutamatergic agent, was conducted on 15 patients with treatment-resistant OCD. Almost half the subjects had a meaningful improvement in symptoms after 12 weeks.[21] Ghaleiha *et al.* reported that memantine combination therapy with fluvoxamine significantly reduced the obsessive–compulsive symptoms as quantified with the Y-BOCS.[12] The effect was evident in the total score and the scores for the Obsession and Compulsion subscales. Adding memantine to fluvoxamine in treatment of OCD also resulted in more complete response in that study.[11] In another case–control study, memantine was found to be effective as a glutamatergic-augmenting agent in severe OCD.[23] An open-label trial by Rodriguez *et al.* assessed the effect of minocycline on nine adult outpatients with Y-BOCS scores ≥16 despite a therapeutic SRI dose.[15] The patients were on stable doses of SRI for at least 12 weeks and other concomitant psychotropic medications for at least 4 weeks prior to the study. In their trial, all patients had failed at least one adequate trial of an antipsychotic in the augmentation of an SRI. The authors showed that minocycline augmentation of SRI pharmacotherapy may not improve OCD in all adult OCD patients, but may improve symptoms in those with early-onset OCD and those with primary hoarding.[15] The difference between the findings of Rodriguez *et al.* and the current trial might be due to the different types of participants between the two trials. Rodriguez *et al.* conducted their study on treatment-resistant patients who had failed at least one adequate trial of an antipsychotic in augmentation with an SRI, whereas the subjects of the current trial were free from any psychiatric medication 6 weeks prior to the study.

In this study, minocycline was administrated with a dosage of 100 mg twice daily with no serious adverse events. The result showed that minocycline significantly reduced OCD symptoms as an adjuvant agent to fluvoxamine in moderate-to-severe OCD patients compared to placebo. Several limitations of this study should be addressed before overgeneralizing its findings. First, the study sample size was relatively small. Second, the follow-up period was short for trials of OCD, which are usually conducted over a 12-week period, and this could partly explain the lower complete response rate (≥35% reduction in

the Y-BOCS score) of this trial (31.9%) compared to a 12-week fluvoxamine trial with a response rate of 45%. A long-term follow-up period is of great importance as OCD is a chronic condition with a high chance of several relapses during the course of the disease.

Conclusion

The results of this 10-week double-blind randomized-controlled trial suggest that minocycline could be a safe and effective adjunctive treatment for more rapid and greater improvement in OCD symptoms. However, safety and efficacy of longer treatment periods with minocycline remain to be determined.

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DISCLOSURE STATEMENT

None of the authors contributing to this article has any conflicts of interest to report.

AUTHOR CONTRIBUTIONS

Z.A., F.R., M.S., and M.R.S. participated in data acquisition and the preparation of the manuscript. M.R.N., S.E., and A.Z. performed data analysis and wrote the manuscript. S.A. designed the manuscript, provided the outlines for the presentation of the study, supervised the study process and edited the final manuscript. All authors have reviewed the process of data analysis, writing of the manuscript and have approved the final article.

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